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May high blood viscosity predict cardiac involvement in COVID-19 patients?

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ABSTRACT

Aims: Assessing the effects of whole blood viscosity (WBV) on prognosis and deterioration in cardiac parameters in COVID-19 patients after recovery using cardiac magnetic resonance imaging (CMRI) and echocardiography is the purpose of this study.

Methods: The study involved 70 patients. Patients who had COVID-19 pneumonia were admitted to the hospital. All patients met the eligibility criteria if they remained symptom-free of respiratory and cardiac symptoms and had negative swab test results at the end of the isolation period, for at least two weeks following the positive swab test result. Transthoracic echocardiography was performed within 24 hours prior to CMRI. WBV was measured in centipoises (cP) at 208 seconds-1 shear rate. The median value of WBV was calculated for the entire study population, which was subsequently utilized to divide the population into two subgroups. These were designated as high WBV and low WBV subgroups.

Results: Elevated levels of hemoglobin, hematocrit, total protein, C-reactive protein, D-dimer, and fibrinogen were observed in individuals with high WBV. Conversely, TAPSE, S', and FAC were notably reduced in those with high WBV. Notably, CMRI revealed significant increases in native T1, native T2 mapping signal, and extracellular volume among patients with high WBV. Furthermore, in individuals with high WBV, there was a significant decrease in right ventricle stroke volume and right ventricle ejection fraction, accompanied by a notable increase in right ventricle end-systolic volume.

Conclusion: WBV values measured during hospital admission may have early and late prognostic importance for COVID-19 infection.

Keywords: Blood viscosity, COVID-19, cardiac MRI, echocardiography

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first appeared in China in 2019 and quickly escalated into a worldwide pandemic. The coronavirus disease 2019 (COVID-19) pandemic has been a major cause of morbidity and mortality on a global scale. Involvement of the respiratory system caused by COVID-19 can range from mild flu to severe pneumonia. Case reports have demonstrated that COVID-19 is also capable of causing cardiac involvement and damage. Proposed pathophysiological mechanisms of cardiac injury include endothelitis, plaque rupture or erosion, stent thrombosis, cardiac stress induced by high cardiac output, myocarditis, heart failure, and arrhythmia.[1,2]

Myocarditis, which encompasses pericarditis, myocardial edema, and myocardial fibrosis, carries a significant risk of adverse outcomes and a poor prognosis.[3-6] The gold standard diagnostic instrument for identifying myocarditis symptoms including inflammation, edema, and fibrosis is cardiac magnetic resonance imaging (CMRI). By employing T1, T2, and extracellular volume (ECV) mapping techniques, CMRI assesses cardiac structure and function and provides a quantitative evaluation of myocardial fibrosis and edema.[7-9] A small study examined patients who recovered from COVID-19 but continued to exhibit cardiac symptoms. In 58% of the patients, CMRI with late gadolinium enhancement (LGE)

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detected persistent cardiac involvement, including fibrosis and myocardial edema.[10] An additional investigation carried out on patients who had recently recovered from COVID-19 and did not exhibit any cardiac symptoms revealed that 78% of the patients had cardiac involvement, while 60% of the patients had persistent myocardial involvement.[11]

The acute respiratory distress syndrome (ARDS) is a clinical manifestation of respiratory failure in patients inflicted with COVID-19. Diffuse alveolar injury, edema, and fibrosis are all components of ARDS. Pulmonary thrombosis, which may involve pulmonary microvessels and lead to pulmonary hypertension, is another potential consequence of ARDS. The right ventricle (RV) afterload may then increase, leading to the development of RV dysfunction.[12,13]

It has been established that whole blood viscosity (WBV) is a significant cardiovascular risk factor and that it fluctuates in a variety of cardiovascular disorders. Patients with acute coronary syndrome undergoing percutaneous coronary intervention and a high WBV are associated with adverse outcomes, including an increased incidence of no-reflow phenomenon, stent thrombosis, and apical thrombus. Patients suffering from acute pulmonary embolism and stroke may also experience negative outcomes.[14-19] There is currently no research in the literature to assess the effect of WBV on the prognosis in patients with COVID-19 and its relationship with the deterioration in cardiovascular parameters after the patients recover. The aim of this study is to evaluate the effects of WBV on prognosis and deterioration in cardiac parameters after recovery in COVID-19 patients, with cardiac MRI and echocardiography which are sensitive tools in the detection of cardiac involvement in patients with COVID-19.

METHODS

Ethics

The research received ethical approval from the local committee (Date: 15.03.2021, Decision No: HNEAH-KAEK 2021/KK/75). Prior to participation, all individuals gave their informed assent. The research was conducted in adherence to ethical guidelines, with particular consideration given to the principles outlined in the Declaration of Helsinki.

Study Design and Study Population

A prospective observational cohort study is being conducted. The research was conducted from April to June of 2020. Seventy patients were included in the study whose upper respiratory tract swab tests were positive for SARS-CoV-2 via reverse transcription-polymerase chain reaction. Patients had no history of chronic disease. The patients were initially committed to the hospital due to COVID-19 pneumonia; however, they were ultimately discharged without requiring non-invasive mechanical ventilation support or further observation in the intensive care unit. All patients were deemed eligible for inclusion in the study fourteen days, provided that they had resolved respiratory symptoms, lacked cardiac symptoms, and had obtained negative swab test results by the end of the isolation period. Patients who declined to participate or who had contraindications for a CMRI were excluded from the study. Prior to CMRI, transthoracic echocardiography (TTE) was conducted within twenty-four hours. Upon the initial admission to the hospital, clinical and demographic information and blood test results were collected. All blood values were determined using conventional, standard procedures. Using the following equation, WBV was calculated in centipoises (cP) at a shear rate of 208 seconds-1: WBV=0.12 X hematocrit (%)+0.17 X plasma proteins (g/L). The median value of WBV was determined for the entire study population, and on the basis of that value, the population of the study was divided into two sub-groups. These were designated as high WBV and low WBV subgroups. The clinical demographic characteristics, biochemical, CMRI and TTE parameters of these two subgroups were compared.

An Echocardiographic Examination

TTE was conducted utilizing a GE Vivid E95 device (Vingmed Ultrasound, Horten, Norway; GE Healthcare) equipped with an M5S probe operating within the frequency range of 1.5-4.6 MHz. A thorough conventional transthoracic echocardiographic examination was conducted in accordance with the current guidelines of the American Society of Echocardiography to assess the structure and function of the heart20. For the computation of the left ventricular ejection fraction (LVEF), the modified biplane Simpson method was utilized. Right ventricular fractional area change (FAC) is calculated using a focused apical view of the RV to determine the area difference between the end-diastolic and end-systolic regions.

Cardiac Magnetic Resonance Imaging

A 1.5-T MR scanner (Signa Explorer; GE Medical Systems, Milwaukee, WI, USA) was utilized to conduct the CMRI; it was equipped with a 32-channel phased-array abdominal coil and electrocardiographic gating. Prior to the CMRI, no intravenous sedation was administered. Breathing instructions were provided to all patients prior to the scan. Two technologists and a radiologist and cardiologist with a combined ten years of experience conducted each examination. The acquisition of sagittal, coronal, and axial localizations within the thorax is achieved via an axial black blood stack employing rapid spin echo to visualize the anatomy of the cardiothorax and steady-state free precession. Then, in order to evaluate cardiac function and volume, a steady-state free precession cine film sequence was obtained, which was balanced along the short and long axes. After acquiring each image set using retrospective gating, twenty cardiac phases were reconstructed. Left ventricular tissue was characterised using T1 mapping with long-T1 5(3)3-shortened modified look-locker inversion recovery and T2 mapping with T2-prepared balanced steady-state free precession. Following the administration of the gadolinium-based contrast agent (0.2 mmol/kg), LGE imaging was performed using a phase-sensitive inversion recovery sequence. The post-contrast T1 mapping sequence was acquired 5 minutes after contrast injection. The late gadolinium enhancement sequence for myocardial scar imaging was acquired 10 and 15 minutes after contrast injection. All sequences were acquired over three segments of the short axis of the left ventricle, from its base to its midpoint and apex.

Each CMRI was interpreted by an experienced cardiologist and an experienced radiologist. CMR image analysis of left ventricular morphology and function was performed

using Circle cvi42 software (Circle Cardiovascular Imaging, Calgary, Canada). Automatic calculation of left and right ventricular volume/function parameters was performed using endocardial and epicardial contours. The quality of late gadolinium enhancement images was assessed visually. Endocardial and epicardial contouring of basal, midventricular and apical short-axis slices was performed for native, post-contrast T1 and T2 mapping. Contamination from blood pools was avoided throughout the epicardial and endocardial boundary contouring process.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, NY). Categorical variables are presented as frequencies and percentages, while continuous variables are reported as means with corresponding standard deviations. Group comparisons for categorical variables were conducted using the Chi-squared test, and for continuous variables with a normal distribution, Student's t-test was employed. The Mann-Whitney U test was utilized for continuous variables without a normal distribution. A p-value less than 0.05 was considered statistically significant.

RESULTS

70 patients (mean age 42.7±10.4 years; 57.1% male) participated in the investigation. 16.62 was the median value of the WBV. On the basis of their WBV value, patients were separated into two groups: those with a low WBV (n=34 patients) and those with a high WBV (n=36 patients). Table 1 presents the baseline clinic and demographic characteristics, and the laboratory findings, of the patients. The characteristics of patients at baseline did not vary between the study groups. Significantly elevated levels of hemoglobin, hematocrit, total protein, C-reactive protein, D-dimer, and fibrinogen were observed in patients with a high WBV. (12.9±1.5 vs 13.8±1.9 p=0.036, 37.9±4.4 vs 41.3±4.7 p=0.003, 67.5±3.8 vs 75.2±3.5 p<0.001, 1.08±1.39 vs 8.1±4.3 p<0.001, 0.31±0.16 vs 1.04±0.72 p<0.001, 418.9±90.7 vs 653.3±103.1 p<0.001 respectively) The rest of the laboratory results were comparable between the two study groups.

The study participants' TTE results are presented in Table 2. Patients who had a high WBV exhibited substantially reduced values for TAPSE, S', and FAC. (26.6±1.1 vs 22.7±1.5 p<0.001, 0.19±0.03 vs 0.12±0.03 p<0.001, 42.5±6.3 vs 34.8±0.9 p<0.001 respectively) Other echocardiographic parameters were not significantly different between study groups.

On CMRI, native T1, native T2 mapping signal and extracellular volume (ECV) were significantly increased in patients with high WBV. (1025.9±3.2 vs 1027.0±0.0 p=0.035, 47.0±2.4 vs 52.6±2.9 p<0.001, 19.62±5.81 vs 38.22±14.64 respectively) Patients with high WBV had right ventricle stroke volume (RVSV) and right ventricle ejection fraction (RVEF) were significantly lower (80.9±14.2 vs 72.9±15.5 p<0.001, 57.9±3.4 vs 49.6±2.5 p<0.001 respectively), but right ventricle end-systolic volume (RVESV) was significantly higher (59.3±13.0 vs 73.9±16.2 p<0.001) (Table 3).

Two patients in the low WBV group and four patients in the high WBV group exhibited LGE (Figure).

Table 1. Baseline characteristics of patients, and laboratory results

	Low WBV group (n=34)	High WBV group (n=36)	p value
Patient characteristics			
Age (years)	43.9±10.8	41.5±10.1	0.338
Gender			0.241
Male (n, %)	17 (%50)	23 (63.9%)	
Female (n, %)	17 (%50)	13 (36.1%)	
BMI (kg/m²)	26.8±3.5	25.9±3.9	0.314
SBP (mmHg)	117.6±13.6	120.5±11.0	0.336
DBP (mmHg)	75.2±7.0	77.6±7.6	0.180
Laboratory Data			
Hemoglobin, g/dl	12.9±1.5	13.8±1.9	0.036
Hematocrit (%)	37.9±4.4	41.3±4.7	0.003
WBV	15.68±0.63	17.38±0.49	<0.001
WBC (10^3/µl)	8.0±4.4	7.5±2.6	0.543
Neutrophil (10^3/µl)	5.6±4.0	5.2±2.6	0.618
Lymphocyte (10^3/µl)	1.8±0.9	1.7±0.8	0.480
Platelet (10^3/µl)	318.2±126.8	298.0±97.64	0.474
Serum creatinine (mg/dl)	0.78±0.12	0.80±0.15	0.668
Glucose (mg/dl)	144.8±71.9	156.1±93.0	0.618
Sodium (mEq/L)	133.7±24.8	138.2±2.9	0.315
Potassium (mEq/L)	4.5±0.4	4.5±0.4	0.555
AST (unit/L)	32.2±21.1	28.8±14.0	0.468
ALT (unit/L)	45.1±47.0	52.0±51.8	0.728
Troponin-T (ng/L)	0.70±1.34	0.87±1.48	0.280
Albumin (g/L)	39.5±4.2	38.7±4.6	0.572
Total protein (g/L)	67.5±3.8	75.2±3.5	<0.001
CRP (mg/dL)	1.08±1.39	8.1±4.3	<0.001
D-dimer (ug/ml)	0.31±0.16	1.04±0.72	<0.001
Fibrinogen (mg/dl)	418.9±90.7	653.3±103.1	<0.001
Prokalsitonin (ng/ml)	0.049±0.051	0.380±1.52	0.377
LDH (unit/L)	247.7±65.0	260.6±71.2	0.475
TSH (mlU/L)	1.5±0.7	1.9±0.9	0.294

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure (mmHg), WBV: Whole blood viscosity, WBC: White blood cell count, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, LDH: Lactate dehydrogenase, TSH: Thyroid stimulating hormone

Table 2. Echocardiography results

	Low WBV group (n=34)	High WBV group (n=36)	p value
Left ventricular end-diastolic diameter (mm)	45.2±2.9	45.6±3.2	0.495
Left ventricular end-systolic diameter (mm)	30.2±2.0	30.8±2.7	0.379
Left atrium anterior-posterior diamater (mm)	30.4±4.1	31.2±4.0	0.327
Left ventricular ejection fraction (%)	57.2±5.2	55.6±4.7	0.089
interventricular septum thickness (mm)	9.3±1.1	9.3±1.1	0.765
posterior wall thickness (mm)	9.3±1.0	9.3±1.1	0.736
E/A ratio	1.15±0.64	1.14±0.60	0.690
Em (cm/s)	0.16±0.05	0.15±0.05	0.265
Am (cm/s)	0.14±0.04	0.12±0.04	0.091
IVRT (ms)	176.9±39.1	185.3±38.4	0.535
IVCT (ms)	74.7±6.8	75.3±8.5	0.766
DT (ms)	176.9±39.1	185.3±38.4	0.535
TAPSE (mm)	26.6±1.1	22.7±1.5	<0.001
S' (cm/s)	0.19±0.03	0.12±0.03	<0.001
FAC (%)	42.5±6.3	34.8±0.9	<0.001

E: mitral inflow early diastolic velocity, A: mitral inflow late diastolic velocity, Em: mitral inflow early diastolic tissue velocity, Am: mitral inflow late diastolic tissue velocity, IVRT: isovolumic relaxation time, IVCT: the isovolumic contraction time, DT: left ventricular deceleration time, TAPSE: tricuspid annular plane systolic excursion S': TDI-derived tricuspid lateral annular systolic velocity wave, FAC: right ventricular fractional area change

Table 3. Cardiac magnetic resonance imaging results

	Low WBV group (n=34)	High WBV group (n=36)	p value
Right ventricle end-diastolic volume	140.2±25.6	149.6± 35.0	0.240
Right ventricle end systolic volume	59.3±13.0	73.9±16.2	<0.001
Right ventricle stroke volume	80.9±14.2	72.9±15.5	<0.001
Right ventricle ejection fraction	57.9±3.4	49.6±2.5	<0.001
T1 map native	1025.9±3.2	1027.0±0.000	0.035
T2 map native	47.0±2.4	52.6±2.9	<0.001
Extracellular volume	19.62±5.81	38.22±14.64	<0.001

WBV: Whole blood viscosity

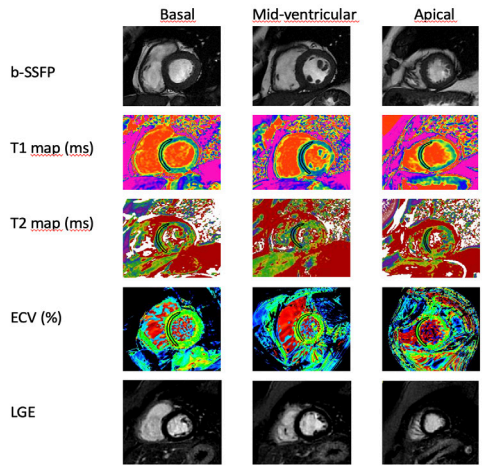

Figure. A 37-year-old male patient diagnosed with COVID-19 underwent cardiac MRI. The same slices of short axis view on basal, mid-ventricular, and apical segment (left to right) for balanced steady state free precession, T1 mapping, T2 mapping, ECV map and LGE images (up-to-down). T1, T2 and ECV mapping values showed increased values for entire ventricle (b-SSFP, balanced steady state free precession; ECV, extracellular volume; LGE, late gadolinium enhancement)

DISCUSSION

COVID-19 has the potential to significantly affect the cardiovascular systems of patients. Morbidity and mortality are more likely to occur in patients with COVID-19 who also have preexisting cardiovascular disease (e.g., coronary artery disease, arterial hypertension, stroke). COVID-19 has been linked to a multitude of cardiovascular complications. COVID-19 has the potential to induce a heightened inflammatory response, upregulate cytokine secretion, and induce a cytokine storm. COVID-19 can induce endotheliitis via vascular inflammation, myocarditis, malign arrhythmias, venous thromboembolism. It is of the utmost importance to comprehend the impact of COVID-19 on the cardiovascular system in order to offer comprehensive medical care to COVID-19 patients and to predict prognoses.[21]

Seventy patients with pulmonary involvement who tested positive for SARS-CoV-2 on swab tests but did not require intensive care unit follow-up or non-invasive mechanical ventilation were included in the study. Patients met the inclusion criteria for the study when they had recovered from COVID-19 infection for a minimum of two weeks. Blood viscosity values were determined using blood samples collected at the time of initial hospital admission. Two categories were formed from the study population based on the median value of WBV. The designations for these two categories are high WBV and low WBV. In addition to CMRI and TTE findings, acute phase reactants over the duration of the disease were compared between these two groups. This is the first report to suggest that cardiac involvement in patients with COVID-19 may be predicted by a high WBV.

Due to the observation of WBV fluctuations in a variety of cardiovascular disorders, it is possible to classify WBV as a significant cardiovascular risk factor. Moreover, high WBV could potentially serve as a risk factor for coronary artery disease. This can occur either indirectly, via its correlation with significant risk factors like arterial hypertension, or directly, by augmenting the resistance generated by the extent of coronary artery constriction. Either way, this would have detrimental consequences for clinical manifestations and maximal myocardial oxygen delivery. Additionally, a high WBV can elevate the probability of stent thrombosis, intraventricular thrombus formation, and no-reflow.[14,22-24] Furthermore, elevated WBV impairs cerebral blood flow and elevates the susceptibility to stroke.[25,26]

An increase in native T2 mapping signal was indicative of myocardial edema, whereas an increase in native T1 mapping signal was indicative of myocardial interstitial fibrosis, according to previous research. The ECV values and native T1 and T2 mapping signals were substantially greater in patients with a high WBV, according to this study. Acute phase reactants, including fibrinogen, D-dimer, and C-reactive protein, were substantially elevated in patients with high WBV. Elevated levels of acute phase reactants may serve as an indicator of an intensified inflammatory response within the body. As a result, our study suggests that diffuse myocardial edema and fibrosis may exist in patients with high WBV.[27-29]

Prior research has demonstrated that RV function may be negatively impacted by ARDS. COVID-19 can induce ARDS

due to the fact that the lungs are among the primary organs affected by SARS-CoV-2; thus, RV may be more susceptible to injury than LV. ARDS can impair the pulmonary circulation through mechanisms other than alveolar injury. These include hypoxic pulmonary vasoconstriction, secretion of vasoconstrictive mediators, extrinsic vascular compression due to interstitial oedema and vascular remodelling. Ultimately, RV failure may result from increased pulmonary vascular resistance and right ventricular afterload.[12,30-32] Patients who were admitted to our study with COVID-19 pneumonia did not develop acute respiratory distress syndrome (ARDS) and did not require follow-up in the intensive care unit. Additionally, we discovered that the RVEDV and RVESV values were greater in the high WBV group on CMRI, whereas the RVEF values were substantially lower. Additionally, RV FAC, TAPSE, and RV S' values, which reflect echocardiographic RV functions, were substantially reduced in the group with a high WBV. An elevation in RV afterload may also occur in patients with COVID-19 pneumonia due to vasoconstriction induced by hypoxia and inflammatory mediators.

Our study demonstrated that WBV measurement at the first hospital admission is associated with higher levels of acute phase reactants values during the course of COVID-19 infection and with impaired right ventricular function parameters with higher T1, T2 and ECV values indicating extensive myocardial fibrosis and oedema when assessed by CMRI and echocardiography after the disease has healed.

Limitations

The results might not be suitable for patients who are younger than 18 years old. Furthermore, these results do not take into account patients with acute COVID-19 infection or those who are asymptomatic at the time of infection.

CONCLUSION

As a result, WBV values measured during hospital admission may have early and late prognostic importance and high WBV may predict cardiac involvement for COVID-19 infection.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Haydarpaşa Numune Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.03.2021, Decision No: HNEAH-KAEK 2021/KK/75).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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